REMARKS

The claims have been amended to clarify the nature and purpose of the invention. Claim 5 has been amended to require that the homopolymer or interpolymer in the temperature-sensitive polymer be formed only from N-(2-hydroxypropyl)methyl acrylamide(lactate)$_n$ where n is 1-10 and may vary in the monomers that constitute the polymer. If n is the same in all of the monomer units – i.e., the resulting polymer is a homopolymer, then the temperature sensitive polymer must also contain a hydrophilic block. However, if n is varied among the monomers and an interpolymer is formed, such coupling to a hydrophilic block is optional. Claim 6 has been canceled.

This amendment clarifies that the polymer does not contain an element formerly thought to be necessary in such polymers, namely poly-N-isopropyl acrylamide (PNIPAAm). As described in paragraphs 40-42 of the present application, prior polymers contained this constituent, but it was realized by the present inventors that the biocompatibility of these polymers was not known (see paragraph 42) and that a favorable system could be based on 2-hydroxypropyl methyl acrylamide-lactate (HPMAm-lactate)$_n$ alone.

Applicants further found that the number of lactate monomers appended as side chains to the polyacrylamide polymer has an effect on the cloud point (CP) (or LCST) and that thus, by varying the number of lactate side chains among the monomers, the LCST of the polymer could be controlled. Further, as the lactate moieties are hydrolyzed by incubation in the body, the LCST becomes higher and thus a drug contained in what was an insoluble polymer can be released due to the enhanced solubility of the polymer below its now higher LCST. This is explained in detail in paragraphs 43-48 of the specification.

As noted in paragraph 45, the monolactate has a much higher LCST than the dilactate; thus, converting the dilactate to the monolactate in some of the monomeric units in a copolymer of the monolactate and dilactate will raise the LCST.

Support for a value of n in the number of lactates appended as set forth in claim 5 is found in paragraph 44, which lists n as 3-10, but it is obvious that the monolactate and dilactate are also possible monomers.

As explained in these paragraphs, by using the appropriate mixture of monomers with varying numbers of lactate appended, the LCST of the polymer can be controlled and changed as some of the lactate side chains are hydrolyzed.

Claim 7 is simply rewritten to be properly dependent from claim 5. Claim 9 is equivalent to paragraph (b) of claim 1 where the variability of n and its ability to effect formation of a hydrogel or micelle if the value of n is varied properly among the monomers in a copolymer results in there being no necessity for a hydrophilic block. Claims 10-11 are similar to claims 6 and 7 but depend from claim 9 rather than claim 5. Claim 12 has simply been rewritten as an appropriate dependent claim from claim 5 as amended; claim 13 is the same as claim 12, but dependent on claim 9.

No new matter has been added and entry of the amendment is respectfully requested. It is understood that this amendment is being submitted after final, but it is believed necessary in order correctly to characterize the invention in accordance with the specification. Applicants respectfully request the Examiner to exercise his discretion and enter the amendment, though made late in prosecution.

Turning, now, to the points raised in the Office action itself:

Priority

Applicants no longer wish to contest priority of the present application in view of the amendment to the claims. Applicants will argue the patentability of the present claims based on the present filing date of 18 March 2004.

The Rejection Under 35 U.S.C. § 112, Paragraph 1

It is believed that the amendments to the claims are responsive to this basis for rejection. Applicants agree that the art only recognizes that polymers are useful for controlled release systems when they are, at least when administered to the subject, hydrogels or micelles. The present polymers are in this form when they are administered to the subject because they are administered at a temperature above the LCST or CP. Of course, it is true, as the Office states, that the polymer will dissolve in water below the LCST. Therefore, it is important to make sure that the controlled release system is administered at a temperature above the LCST where the polymer is not soluble. The polymers of the invention permit this because they are designed to be administered above their LCST. It is only after incubation in the subject that the LCST is raised and therefore the polymers become soluble.

There are basically two ways to provide for an LCST in the appropriate temperature range to makes its use in controlled drug release possible. One of these is that recognized to the Office – *i.e.*, the construction of polymers wherein hydrophobic blocks are coupled to hydrophilic blocks. Claims that require hydrophilic blocks and thus form hydrogels or micelles have not been questioned as to enablement. Thus, there should be no question that claims 7-8 and 10-11 (i.e., 11 as now amended) are free of this rejection.

Then the question becomes whether it is possible to construct a polymer with the appropriate LCST when no specific "hydrophilic block" is included. The way this is done is explained in paragraphs 42-49 in the specification. Thus, by using an interpolymer with a correct distribution of monomers, no separate hydrophilic block is necessary; only if the polymer is a homopolymer (or a poorly designed interpolymer) is that required. Thus, claim 5 now requires that if the polymer is a homopolymer of N-(2-hydroxypropyl) methyl acrylamide $(lactate)_n$ this polymer must be coupled to a hydrophilic block. However, as in claim 9 where n is varied, the interpolymer can form a hydrogel or micelle on its own.

It is believed the amendments to the claims and the reference to specification make this clear. Accordingly, this basis for rejection may be withdrawn.

The Art Rejections

Claims 5-7 were rejected as assertedly unpatentable over Neradovic, *et al., Macromolecules* (2001) 34:7589-7591. In view of the amendment to the claims, this basis for rejection can be withdrawn. As noted, Neradovic, which is the work of the same group represented by applicants herein, require diblock copolymers which include polyNIPAAm. PolyNIPAAm is now excluded from the claims. The accomplishment of the present invention is to provide polymers that successfully are able to exclude this component.

Claims 9 and 10 were rejected as assertedly obvious over Neradovic in view of Heller (5,939,543). The claims are free of this rejection for the same reason as set forth with regard to Neradovic alone. Neradovic does not suggest the possibility of polymers in this context consisting only of N-(2-hydroxypropyl) methyl acrylamide $(lactate)_n$.

Applicants note that claims 8 and 12 as previously presented do not appear to be subject to rejection either over the art or as lacking enablement.

Conclusion

The claims have been amended to clarify the invention as permitting construction of temperature-sensitive polymers that are useful for controlled drug release which consist only of monomers of N-(2-hydroxypropyl) methyl acrylamide that contain lactate side chains of varying lengths. By varying the lengths of the lactate side chains, the LCST can be adjusted to an appropriate level so that the compositions can be administered above their LCST and converted *in vivo* to forms where the LCST is raised so that their environment is now below this critical temperature and the contained drugs are released. None of the cited art suggests the polymers as now claimed. Therefore, applicants believe claims 5 and 7-13 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor problems remain that might be resolved over the telephone, a call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 313632001120.

Respectfully submitted,

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